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Gut-Brain Axis and Neurodegeneration: Mechanisms, Evidence, and Therapeutic Potential

Adtiya Verma, Ansh Rihal, Shivam, Arti Rana*, Ashish Sharma

DDM College Of Pharmacy Gondpur Banehra Una Himachal Pradesh.

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ABSTRACT

Neurodegenerative diseases are a major global health challenge, affecting millions and imposing heavy socioeconomic costs on healthcare systems. Historically, research has focused mainly on intracranial pathological processes. The emergence of the microbiota-gut-brain axis (MGBA) has, however, substantially revised our perspective on the origins of neurodegenerative disorders. This in-depth review synthesizes mechanistic insights, clinical data, and therapeutic avenues related to the MGBA in conditions such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS). The MGBA comprises interrelated components linking the gastrointestinal tract and the central nervous system (CNS), communicating through the vagal and other neural routes, immune signaling cascades, endocrine pathways, and microbe-derived metabolites. Dysbiosis—defined as shifts in the composition and abundance of gut microbes—has been identified as a prominent pathological feature across neurodegenerative disorders. Key mechanistic connections between dysbiosis and neurodegeneration include: disruption of the intestinal barrier leading to heightened permeability and systemic exposure to lipopolysaccharides (LPS) and microbial metabolites; compromise of the blood-brain barrier (BBB) permitting peripheral immune infiltration and entry of neurotoxic substances; activation of microglia and neuroinflammatory responses driven by loss of short-chain fatty acids (SCFAs) and increased pro-inflammatory mediators; and direct promotion of pathological protein misfolding via bacterial amyloid cross-seeding. Clinical research indicates that dysbiotic shifts often occur before clinical symptoms in AD and PD, with microbial profiles correlating with disease severity. Animal experiments provide strong causal evidence: fecal microbiota from affected patients transferred to germ-free mice accelerates neurodegenerative pathology.

INTRODUCTION

Background and Clinical Significance

***Corresponding Author:** Arti Rana
Address: *Associate Professor DDM College Of Pharmacy Gondpur Banehra Una Himachal Pradesh*
Email ✉: Ranaarti63@gmail.com

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Neurodegenerative disorders impose a heavy global health toll, affecting millions and generating significant economic and social strain on medical services [1,2]. Despite intensive research efforts, the origins and progression of these illnesses are not yet fully understood. Traditional paradigms have emphasized brain-centered pathologies including protein misfolding, mitochondrial deficits, oxidative damage, and neuroinflammation within the CNS [1]. The recognition of the microbiota-gut-brain axis has shifted this view, highlighting how pathological events in the gastrointestinal tract can meaningfully impact cerebral health and disease susceptibility [1,2]. The gut microbiome—an immense community of bacteria, viruses, archaea, and fungi—represents a complex ecological system that actively shapes human physiology [2]. Rather than passive inhabitants, these microorganisms influence immune status, metabolic balance, neurotransmitter production, and barrier function [2]. Dysbiosis, referring to both compositional and functional disturbances of this microbial community, has increasingly been implicated in the initiation and progression of neurodegenerative diseases [1,2].

Significance of Microbiota-Gut-Brain Axis in Neurodegeneration

Recent clinical findings provide substantial links between the MGBA and neurodegenerative disease. Microbial alterations have been detected during preclinical and prodromal periods in AD and PD, suggesting dysbiosis can precede clinical onset [1,2]. Experimental animal work shows that changing gut microbial composition can directly modify neurodegenerative disease trajectories, supporting a causal relationship beyond mere association [1,2]. These insights have opened new therapeutic directions that target the gut microbiota to prevent or slow neurodegeneration.

Components and Communication Pathways of the Microbiota-Gut-Brain Axis

Anatomical and Functional Components

The MGBA integrates multiple anatomical and functional elements spanning the gut and the CNS [2]. Central to this system are the gut microbes—billions to trillions of commensals mainly inhabiting the colon [2]. The intestinal mucosa acts as the primary interface between microbes and host, composed of a single epithelial cell layer sealed by tight junction proteins that prevent bacterial translocation [2]. This barrier is reinforced by a mucus layer and resident immune cells that continuously survey luminal contents [2]. The enteric nervous system (ENS), often called the "second brain," houses roughly 500 million neurons distributed within the gastrointestinal tract [1]. The ENS operates with a degree of autonomy while maintaining extensive bidirectional communication with the CNS via neural and humoral channels [1]. Situated beneath the epithelium, gut-associated lymphoid tissue (GALT) orchestrates immune surveillance through dendritic cells and lymphocytes that sample microbial antigens [2].

Neural Pathways: The Vagus Nerve and Beyond

The vagus nerve is the main neural conduit mediating microbiota-to-brain signals [3]. Composed of about 80% sensory (afferent) and 20% motor (efferent) fibers, vagal afferents relay signals from intestinal receptors to brainstem and higher centers [3]. These afferents detect mechanical stretch, nutrient cues, and microbial metabolites, activating brainstem nuclei that regulate appetite, mood, and autonomic outputs [3]. Vagal efferents transmit central signals that adjust gut secretion, motility, and local immune functions [3]. Importantly, gut microbes can directly drive vagal signaling by producing neuromodulators such as γ-aminobutyric acid (GABA), serotonin (5-HT), and histamine that stimulate vagal afferents or ENS neurons [3]. This provides a rapid pathway for microbial metabolites to impact brain activity [3]. In addition to the vagus , sympathetic and spinal afferent nerves convey visceral sensory information and modulate intestinal immune processes [2]. Together, these neural layers enable swift bidirectional communication allowing the brain to sense and respond to microbiota-derived signals within seconds to minutes.

Immune Pathways

Immune signaling constitutes a central MGBA communication route [1,2]. Dysbiosis-driven changes in microbial communities alter production of immune-modulating compounds, typically shifting toward a pro-inflammatory state [1,2]. Overgrowth of Gram-negative bacteria during dysbiosis increases lipopolysaccharide (LPS) levels, which can cross a weakened epithelial barrier and activate pattern recognition receptors such as toll-like receptor 4 (TLR4) on immune cells [4]. Activated intestinal immune cells—including dendritic cells and macrophages—secrete pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and interleukin-8 (IL-8) [1,4]. These cytokines circulate systemically, accessing the brain where they stimulate resident CNS immune cells—chiefly microglia—inducing widespread neuroinflammation [1]. Dysbiosis also reduces regulatory T cell (Treg) numbers that normally restrain inflammation, further skewing immune balance toward pathogenic pro-inflammatory responses [5].

Endocrine and Metabolic Pathways

The gut microbiota exerts strong effects on endocrine signaling via several mechanisms [2]. Dysbiotic shifts alter circulating neuroendocrine hormones including peptide YY (PYY), glucagon-like peptide-1 (GLP-1), and serotonin [2]. SCFAs generated by bacterial fermentation of dietary fiber stimulate colonic cells to release PYY and GLP-1, which send signals to the brain to regulate appetite, glucose control, and metabolism [2]. Serotonin illustrates the microbiota's role in neurotransmitter regulation: roughly 90% of the body's serotonin is synthesized in the gut by enterochromaffin cells, and certain commensals—particularly spore-forming Firmicutes—enhance intestinal serotonin production [1]. Loss of SCFA-producing bacteria in dysbiosis reduces systemic serotonin, with potential consequences for mood, cognition, and motor control [1]. The hypothalamic-pituitary-adrenal (HPA) axis is another route by which the microbiota affects brain function [2]. LPS translocation from a compromised gut activates the HPA axis, elevating corticosterone and adrenocorticotropic hormone (ACTH) levels [2]. Chronic stress hormone elevation sustains neuroinflammatory processes and may promote neurodegeneration [2].

Microbial Metabolites: Short-Chain Fatty Acids and Beyond

Short-chain fatty acids (SCFAs)—mainly acetate, propionate, and butyrate—produced by bacterial fermentation of fiber are among the most influential microbiota-derived metabolites [6,7]. SCFAs can traverse the BBB and exert neuroprotective actions through G-protein coupled receptors (notably GPR41 and GPR43) [8]. They support regulatory T cell differentiation, suppress pro-inflammatory T cell responses, and directly regulate microglial activity [6,8]. At the molecular level, SCFAs act as histone deacetylase (HDAC) inhibitors, modifying gene expression in immune and glial cells to favor anti-inflammatory states [6]. SCFAs upregulate anti-inflammatory cytokines such as interleukin-10 (IL-10) while downregulating pro-inflammatory mediators [6,8]. Nonetheless, SCFA effects are nuanced and context-dependent—while certain SCFAs are neuroprotective in some scenarios, specific metabolites can, under particular conditions, exacerbate pathological processes like protein aggregation [2]. Beyond SCFAs, the microbiota produces a diverse array of bioactive molecules including tryptophan derivatives (e.g., indoles, kynurenine metabolites), secondary bile acids, and phenolic compounds [2,7]. Microbial metabolism of tryptophan generates ligands that activate the aryl hydrocarbon receptor (AhR) on intestinal and immune cells, promoting barrier function and anti-inflammatory responses [2]. Dysbiosis-driven reductions in these beneficial metabolites weaken intestinal integrity and disturb CNS immune homeostasis [2].

Mechanistic Pathways Linking Dysbiosis to Neurodegeneration

Intestinal Barrier Dysfunction and Increased Permeability

The intestinal epithelial barrier is the key boundary controlling interactions between luminal microbes and the host immune system [4]. Comprised of a single epithelial cell layer joined by tight junction proteins—claudins, occludin , and zonula occludens-1 (ZO-1)—it tightly regulates paracellular transport [4]. Dysbiosis alters microbial metabolites and species composition in ways that undermine barrier integrity through several mechanisms [9,4]. Dysbiotic microbiota often produce more pro-inflammatory LPS while reducing SCFA-producing taxa [9,4]. Loss of SCFAs impairs epithelial energy metabolism and diminishes HDAC inhibition necessary for maintaining tight junctions [4]. Additionally, decreases in mucus-secreting bacteria thin the protective mucus layer, increasing direct microbial contact with epithelial cells [4]. The net result is heightened intestinal permeability—commonly termed “leaky gut”—permitting bacterial LPS, bacterial amyloids, and other harmful factors to enter the circulation [9,4]. This increased permeability sets off a pathological cascade: circulating LPS activates peripheral immune cells, systemic pro-inflammatory cytokines reach and compromise the BBB, and dysbiosis-associated metabolic byproducts circulate systemically [4,5]. In individuals with neurological susceptibility, these systemic inflammatory and metabolic disturbances can trigger or hasten neurodegenerative processes [5].

Blood-Brain Barrier Disruption and CNS Immune Infiltration

The BBB preserves CNS homeostasis by selectively blocking peripheral immune cells and circulating molecules from entering the brain parenchyma [9,5]. Systemic inflammation and LPS translocation caused by dysbiosis activate BBB endothelial and perivascular immune cells, increasing BBB permeability [9,5]. Multiple cellular mechanisms underlie BBB breakdown [5]. Circulating pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) engage cytokine receptors on BBB endothelial cells, inducing upregulation of adhesion molecules (ICAM-1, VCAM-1) and matrix metalloproteinases (MMPs) [5]. MMPs degrade tight junction proteins, further increasing BBB leakiness [5]. Concurrently, dysbiosis-related reduction in Tregs and a rise in effector T cells (Th1 and Th17) fosters T cell migration across the BBB through adhesion molecule and chemokine expression [5]. Once the BBB is compromised, peripheral immune cells—monocytes, macrophages, and T cells—enter the brain, intensifying neuroinflammation and neuronal injury [5]. Clinical evidence shows elderly individuals with cognitive impairment and dysbiosis have greater hippocampal BBB permeability inversely correlated with the abundance of SCFA-producing bacteria [9].

Microglial Activation and Neuroinflammation

Microglia are the CNS's resident innate immune cells, acting as frontline detectors of pathological signals [1]. While typically surveillance-oriented, microglia can be driven into pro-inflammatory M1 states by dysbiosis-associated peripheral immune activation, LPS translocation, systemic cytokines, and loss of microbiota-derived metabolites [1]. Activated microglia produce pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), chemokines (CCL2, CXCL1), and reactive oxygen species (ROS) via NLRP3 inflammasome activation [1,4]. This inflammatory environment harms neurons through oxidative stress, synaptic dysfunction, and apoptosis induction [1]. Chronic microglial activation and ensuing neuroinflammation are central pathological features across major neurodegenerative diseases [1]. Recent work indicates SCFAs and other microbial metabolites directly influence microglial states [6]. SCFAs dampen microglial pro-inflammatory signaling by inhibiting NF- κB pathways and HDAC-dependent gene programs, and they promote transitions toward anti-inflammatory M2 phenotypes [6]. Therefore, loss of SCFA-producing organisms is a pivotal mechanism by which dysbiosis fosters microglial activation and CNS inflammation [1,2].

Protein Misfolding and Aggregation

New data reveal direct links between dysbiosis and the misfolding of proteins that characterize neurodegenerative diseases [10,11]. Certain gut microbes produce biofilm-associated proteins (BAPs) with amyloidogenic regions that assemble into amyloid-like fibrils within the intestinal lumen [10]. Metagenomic studies find that the prevalence of BAP-encoding genes in the gut correlates with Parkinson's disease rates in populations [10]. Mechanistically, BAP-derived amyloids can interact with neuronal α-synuclein via cross-seeding, where microbial amyloids act as nucleation sites accelerating α-synuclein misfolding and aggregation [10,11]. In vitro, preformed BAP amyloid fibrils promote α-synuclein fibrillization at concentrations where α-synuclein alone does not aggregate, offering direct evidence for cross-seeding [10]. Intracellular BAP amyloids can also disrupt chaperone-mediated autophagy, undermining protein quality control [10]. In vivo, mice introduced with BAP-derived amyloid fibrils into the brain develop features of Parkinson's disease, including α-synuclein aggregation, neuroinflammation, and loss of dopaminergic neurons [10]. These results suggest that expansion of BAP-producing bacteria in dysbiosis may initiate or worsen PD through mechanisms that are not solely driven by systemic inflammation [10]. Likewise, LPS from dysbiotic microbiota may facilitate amyloid-beta aggregation and tau pathology in AD via TLR4 activation of microglia and astrocytes, NF- κB-mediated increases in amyloid-beta production, and disruption of proteolytic clearance pathways [4].

Alzheimer's Disease and the Microbiota-Gut-Brain Axis

Microbiota Alterations in Alzheimer's Disease

Numerous clinical investigations have reported distinct dysbiotic signatures in AD patients versus cognitively intact controls [1,2]. These include diminished microbial diversity, loss of SCFA-producing genera (notably Faecalibacterium and Roseburia), and enrichment of potentially pathogenic Gram-negative taxa [1,2]. Longitudinal data indicate these microbiota changes can precede cognitive symptoms in individuals who later develop AD, supporting a contributory role for dysbiosis beyond dementia-related lifestyle changes [1]. The pattern of microbiota disruption in AD points to mechanisms linked to disease biology [4]. Reduced SCFA-producing bacteria lead to lower systemic and local SCFA concentrations [9,4]. Given SCFAs' roles in modulating microglia, preserving BBB function, and maintaining peripheral immune tolerance, an SCFA deficit plausibly drives AD-related pathology [6,9].

Mechanisms Linking Dysbiosis to Alzheimer's Pathology

Multiple mechanistic routes connect dysbiosis to amyloid-beta and tau abnormalities central to AD [1,4]. The LPS hypothesis posits that dysbiosis-driven Gram-negative expansion raises circulating LPS, which crosses a leaky intestinal barrier and chronically stimulates TLR4 on peripheral immune cells and microglia [4]. LPS-mediated TLR4 activation of microglia enhances expression of β-secretase and γ-secretase—enzymes that cleave amyloid precursor protein (APP) into amyloid-beta peptides [4]. LPS also triggers NF-κB-driven increases in pro-inflammatory cytokines that promote amyloid-beta production and impede its clearance [4]. Tau hyperphosphorylation is similarly exacerbated by LPS-driven neuroinflammation via GSK3-beta activation [4]. SCFA deficiency in dysbiosis contributes to AD through additional pathways [9,4]. The hippocampus is particularly reliant on SCFA-mediated protection; reductions in SCFAs heighten hippocampal vulnerability to amyloid toxicity and impair synaptic plasticity through diminished HDAC inhibition [9]. SCFA loss also fosters microglial activation and diminishes tolerogenic antigen-presenting cells, tilting immune responses toward inflammation that favors amyloid accumulation [6,8].

Blood-Brain Barrier Integrity in Alzheimer's Disease

Recent findings suggest BBB disruption is an early event in the progression toward AD and may occur before overt amyloid deposition [9,5]. Systemic inflammation and circulating LPS from dysbiosis activate BBB endothelial cells, increasing permeability and permitting amyloid-beta and other neurotoxic molecules to enter the brain [9]. Simultaneously, heightened BBB permeability allows peripheral immune cells to infiltrate and amplify neuroinflammation [9,5]. Clinical studies show inverse relationships between hippocampal BBB permeability and cognitive function in older adults with dysbiosis, and depletion of SCFA-producing bacteria (particularly Faecalibacterium and Oscillospira) correlates strongly with reduced BBB integrity [9]. These data imply that dysbiosis-driven BBB breakdown is a pivotal mechanism connecting gut alterations to cognitive decline in AD [9].

Parkinson's Disease and the Microbiota-Gut-Brain Axis

The Gut-Origin Hypothesis of Parkinson's Disease

A persuasive model posits that Parkinson's disease may begin in the gut, with pathological α-synuclein aggregates forming initially in enteric neurons and then propagating to the brain via vagal pathways [1,12]. Supportive evidence includes reduced PD risk in vagotomized patients, detection of α-synuclein inclusions in enteric neurons years before central changes in PD patients, and animal studies showing α-synuclein applied to the vagus nerve can spread to the brain in a prion-like manner [1,12]. Dysbiosis likely initiates these processes through several mechanisms [12,10,11]. As noted, expansion of BAP-producing bacteria in dysbiosis fosters α-synuclein aggregation by cross-seeding [10]. Concurrent intestinal barrier dysfunction allows bacterial amyloids and LPS to enter the circulation and affect the enteric nervous system and its BBB-like barriers [1,12].

Microbiota Alterations in Parkinson's Disease

PD patients display characteristic dysbiotic profiles, including reduced microbial diversity, loss of beneficial SCFA-producing taxa, and enrichment of potentially harmful Gram-negative bacteria [1,2,12]. Multiple studies link dysbiosis severity with PD progression, especially reductions in specific SCFA-producing organisms [1,12]. These microbial shifts often appear before motor symptoms in prodromal PD, reinforcing a pathogenic role [1]. The nature of dysbiosis in PD suggests direct ties to α-synuclein aggregation and dopaminergic neuron vulnerability [1,12]. Declines in dopamine-producing bacteria perturb peripheral dopamine metabolism, whereas growth of pro-inflammatory microbes fosters inflammation that selectively impacts dopaminergic neurons [1,12]. Dysbiosis-driven alterations in tryptophan metabolism also reduce production of AhR ligands, weakening intestinal barrier defenses and promoting systemic immune activation [2].

olecular Mechanisms of Dysbiosis in Parkinson's Pathogenesis

Several molecular mechanisms link dysbiosis to PD [1,12,11]. The cross-seeding model posits that BAP amyloids from dysbiotic bacteria initiate α-synuclein aggregation through nucleation-dependent processes [10,11]. Dysbiosis-related barrier breakdown permits LPS and bacterial amyloids to translocate, eliciting systemic and enteric neuroinflammation [1,12]. Loss of bacteria that synthesize dopamine impairs local dopamine availability, influencing immune tolerance via dopaminergic signaling on enteric immune cells and promoting pro-inflammatory responses [1]. Additionally, dysbiosis-driven SCFA depletion disrupts microglial regulation and encourages pro-inflammatory microglial states [1,6].

Other Neurodegenerative Disorders and the Microbiota-Gut-Brain Axis

Multiple Sclerosis and Dysbiosis

Multiple sclerosis, traditionally viewed as an autoimmune demyelinating disease, also displays clear connections to dysbiosis [1,2,8]. MS patients show microbiota shifts characterized by reduced SCFA-producing organisms, increased Gram-negative LPS-producing bacteria, and loss of taxa that foster immune tolerance [1,8]. Evidence links dysbiosis to MS pathogenesis: SCFA-deficient microbiota impair Treg development and favor pro-inflammatory Th1 and Th17 responses that drive CNS autoimmunity [8]. Dysbiosis-associated intestinal barrier compromise permits LPS translocation, sustaining systemic immune activation [8]. Importantly, circulating SCFA levels are significantly lower in active progressive MS patients versus controls, and clinical severity correlates with SCFA deficiency [8].

Amyotrophic Lateral Sclerosis and Dysbiosis

ALS patients exhibit dysbiotic microbiota with reduced diversity and altered metabolic capacities [1,2]. Mechanistic studies indicate dysbiosis promotes neuroinflammation particularly damaging to motor neurons, with changes in amino acid metabolism—especially disturbances in glutamate and glycine balance—contributing to excitotoxic injury of motor neurons [2].

Clinical and Experimental Evidence for Dysbiosis in Neurodegeneration

Human Clinical Studies

A breadth of cross-sectional and longitudinal clinical research ties dysbiosis to neurodegenerative disease [1,2,9]. Microbiome shifts have been observed in preclinical and prodromal stages of major neurodegenerative disorders, implying dysbiosis can precede symptomatic disease [1,2]. Microbial composition correlates with clinical severity in AD, PD, and MS, with the degree of dysbiosis predicting cognitive and motor decline [1,2]. Advanced metabolomic and microbiota analyses reveal that

SCFA deficiency associated with dysbiosis correlates with increased BBB permeability and cognitive impairment in older adults [9]. These clinical findings establish dysbiosis as a salient pathological feature of neurodegeneration with possible therapeutic relevance [9].

Preclinical Animal Models

Animal models offer strong causal evidence that dysbiosis promotes neurodegeneration [1,2]. Germ-free mice lacking microbiota or antibiotic-treated animals with depleted microbiomes demonstrate delayed onset and milder disease in multiple neurodegenerative models, indicating that the microbiota is required for full disease expression [1,2]. Conversely, transferring dysbiotic microbiota from AD or PD patients into germ-free mice accelerates pathology compared with transfer from healthy donors [1,2]. Such experiments robustly support causality: dysbiosis can drive neurodegenerative processes rather than just reflect disease-related behavioral changes [1,2].

Therapeutic Approaches Targeting the Microbiota-Gut-Brain Axis

Probiotics and Psychobiotics

Probiotics—live microbial strains administered therapeutically—are one strategy to correct dysbiotic microbiota composition [1,13,14]. Multiple randomized trials indicate that multistrain probiotic supplementation can alter the Firmicutes/Bacteroidetes balance, strengthen intestinal barrier function, reduce neuroinflammation, and slow cognitive decline in both experimental models and patients [1,13]. Psychobiotics denote probiotics selected for their neuromodulatory capacities [1]. Certain Lactobacillus and Bifidobacterium species produce GABA, serotonin precursors, and other neuroactive compounds that directly affect brain function [1]. Clinical studies report that psychobiotic supplementation can decrease anxiety, improve mood, and enhance cognition in healthy individuals and in patients with neurological conditions [1,13].

Mechanisms through which probiotics provide neuroprotection include: (1) SCFA generation via fermentation of dietary fiber; (2) direct synthesis of neuroactive metabolites; (3) reinforcement of barrier integrity through support of tight junction proteins; (4) competitive exclusion of dysbiotic pathogens for ecological niches; and (5) immune modulation by promoting Treg differentiation and IL-10 production [1,13].

Prebiotics and Dietary Interventions

Prebiotics—non-living food components that selectively stimulate beneficial microbes—complement probiotic strategies [1,13]. Fibers like inulin, fructooligosaccharides (FOS), and resistant starch serve as substrates for SCFA-producing bacteria [1,13]. Prebiotic supplementation raises fecal SCFA levels, improves cognition, and lowers neuroinflammation in experimental settings [1,13]. Diet exerts a major influence on microbiota composition and function, impacting neurodegeneration risk [1,2]. Mediterranean-style diets rich in fiber, polyphenols, and fermented foods favor SCFA-producing microbes, while Western diets high in processed foods and low in fiber promote dysbiosis [1,2,4]. Epidemiological studies link adherence to Mediterranean diets with reduced incidence of AD and PD, potentially via microbiota-mediated mechanisms [1,2].

Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT)—transfer of fecal material from healthy donors to recipients—represents an intensive approach to remodel a recipient's microbial community [13,15,14]. FMT is established as standard care for recurrent Clostridioides difficile infection and is under investigation for neurological diseases including AD, PD, MS, and ALS [13,15,14]. Mechanistic studies in rodents show that FMT from healthy donors to dysbiotic neurodegeneration models markedly improves cognition and motor function, reduces pathological protein aggregation, and attenuates neuroinflammation [13,15]. These benefits appear to stem from restoration of SCFA-producing bacteria, improved barrier function, lowered circulating LPS, and reestablishment of immune tolerance [13,15]. In humans, preliminary FMT studies in hepatic encephalopathy—a neurological condition driven by dysbiosis-related hyperammonemia—demonstrate cognitive improvement and reduced systemic inflammation [13]. Despite encouraging preclinical data, randomized controlled trials of FMT in AD, PD, and ALS are limited, though ongoing studies will help clarify its therapeutic value [13,15,14].

Additional Microbiota-Modulating Therapies

Beyond probiotics, prebiotics, and FMT, emerging interventions include targeted small-molecule modulators of the microbiota, aryl hydrocarbon receptor (AhR) agonists that enhance barrier integrity and immune tolerance, and selective SCFA supplementation [1,2]. Some approaches investigate short-term targeted antibiotics to remove dysbiotic pathogens before introducing probiotics [1,13]. Vagal nerve stimulation (transcutaneous or surgical) is another strategy to boost parasympathetic signaling and activate cholinergic anti-inflammatory pathways, potentially synergizing with microbiota-targeted therapies [1]. Preliminary studies combining probiotics with transcutaneous vagal stimulation report additive cognitive benefits compared with either treatment alone [16].

Current Challenges and Future Directions

Challenges in Translation to Clinical Practice

Despite compelling preclinical and emerging clinical evidence, implementing microbiota-targeted therapies for neurodegeneration faces multiple obstacles [1,2]. Inter-individual variability in microbiomes is pronounced, with diverse dysbiotic patterns found among people sharing the same neurodegenerative diagnosis [1,2]. This heterogeneity calls for precision medicine approaches that tailor microbiota interventions to individuals rather than relying on uniform treatments [1,2]. Establishing direct causality between specific dysbiotic traits and neurodegenerative pathology remains incomplete; although dysbiosis-targeted treatments are promising, definitive controlled trials demonstrating disease modification in human neurodegenerative populations are scarce [1,2]. Mechanistic diversity is substantial: within a single disorder like AD, dysbiosis may drive pathology via distinct mechanisms across different patients [1,2].

Need for Personalized and Precision Medicine Approaches

Future clinical translation will require precise microbiota profiling to pinpoint dysbiotic features most relevant to an individual patient's disease process [1,2]. Multi-omics strategies integrating genomic, metagenomic, metabolomic, and treatment-response data are needed to support bespoke microbiota modulation plans [1,2]. Longitudinal biomarker-guided studies could identify dysbiotic signatures that strongly predict neurodegenerative progression, enabling early detection of high-risk individuals who might benefit from preventive microbiota interventions [1,2]. Determining optimal timing for intervention (preventive, early, or late-stage) and evaluating combination therapies (e.g., probiotics + prebiotics + dietary change) require systematic testing in rigorously designed clinical trials [1,2].

FUTURE RESEARCH DIRECTIONS

Research priorities should include: first, mechanistic studies that delineate precise molecular pathways by which specific bacterial taxa and metabolites influence neurodegeneration, facilitating rationally targeted interventions [1,2]; second, large prospective cohorts tracking microbiome dynamics from midlife through disease onset to clarify temporal relationships and identify critical intervention windows [1,2]; third, development of standardized microbiota profiling methods and reference repositories to enable cross-study comparisons and identification of reproducible dysbiotic patterns [1,2]; fourth, exploration of microbiota-based biomarkers for early diagnosis, prognosis, and monitoring treatment response to support precision approaches [1,2]; and finally, well-powered phase 2 and 3 clinical trials of microbiota-modulating therapies in clearly characterized neurodegenerative populations to establish clinical efficacy [1,2].

CONCLUSION

The microbiota-gut-brain axis offers a unifying framework demonstrating that peripheral gastrointestinal events exert significant effects on brain health and susceptibility to neurodegeneration. Dysbiosis—marked by decreased microbial diversity, loss of SCFA-producing bacteria, and enrichment of pro-inflammatory taxa—has emerged as a common pathological element across diseases including AD, PD, MS, and ALS. Mechanistic links from dysbiosis to neurodegeneration include intestinal barrier breakdown and increased permeability, BBB compromise and peripheral immune infiltration, microglial activation with ensuing neuroinflammation, and direct facilitation of pathological protein misfolding via bacterial amyloid cross-seeding. Clinical and experimental findings show dysbiotic changes can precede clinical symptoms and correlate with disease severity, with animal models demonstrating causality through microbiota transfer. Therapeutic approaches targeting the MGBA—probiotics and psychobiotics, prebiotics and dietary modification, FMT, and novel strategies like targeted metabolite supplementation and vagal stimulation—hold substantial promise. However, clinical adoption faces challenges such as inter-individual microbiome variation, incomplete mechanistic understanding, and limited large-scale randomized trials. Advancing the field will require precision medicine informed by multi-omics, rigorous trials to establish optimal timing and combinations of interventions, and systematic delineation of disease-specific dysbiotic signatures. Targeting the gut microbiota may provide accessible, non-invasive avenues to prevent and treat neurodegenerative diseases and potentially alter their course. The MGBA signifies a pivotal shift in our understanding of neurodegeneration, underscoring how peripheral processes shape CNS health. Continued investigation into this bidirectional system is likely to surface novel therapeutic targets and strategies to prevent and treat neurodegenerative diseases, ultimately improving outcomes for millions worldwide.

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